

# PATENT COOPERATION TREATY

**PCT**

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 14 January 1999 (14.01.99)	
<b>International application No.</b> PCT/IL98/00254	<b>Applicant's or agent's file reference</b> IPL-8 PCT
<b>International filing date (day/month/year)</b> 01 June 1998 (01.06.98)	<b>Priority date (day/month/year)</b> 02 June 1997 (02.06.97)
<b>Applicant</b> MESSIKA, Ziva et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
20 December 1998 (20.12.98)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland	<b>Authorized officer</b> Yolaine CUSSAC
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>IPL-8 PCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/IL 98/ 00254</b>	International filing date (day/month/year) <b>01/06/1998</b>	(Earliest) Priority Date (day/month/year) <b>02/06/1997</b>
Applicant  <b>INTERPHARM LABORATORIES LTD. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ **Certain claims were found unsearchable** (see Box I).

2. ☐ **Unity of invention is lacking** (see Box II).

3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

☒ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the **title**, ☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

Figure No. \_\_\_\_\_ ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL 98/00254

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 98/00254

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/28 C07K14/525 A61K38/19 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KORN J.H. ET AL.: "Cloning of genomic DNA for Tumor Necrosis Factor and efficient expression in CHO cells" LYMPHOKINE RESEARCH, vol. 7, no. 4, 1988, pages 349-358, XP002078184 cited in the application see the whole document ----- -/--	1-6

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## ° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

21 September 1998

Date of mailing of the international search report

01/10/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Macchia, G

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 98/00254

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 168 214 A (GENENTECH INC.; AGGARWAL B.B. ET AL. (US)) 15 January 1986 cited in the application see page 8, line 12-14 see page 9, line 5-18 see page 12, line 25-30 see page 15, line 32 - page 16, line 15 see page 26, line 18-20 see page 28, line 1 - page 31, line 13 see page 66, line 29-31 see page 68 - page 69; example 26 ----	1-6
X	WO 88 06625 A (CETUS CORPORATION; MARK D.F. ET AL. (US)) 7 September 1988 see page 8, line 11-32 see page 13, line 12-20 see page 20, line 29 - page 23, line 6 ----	1-3,5,6
X	KAKU NAKAGAWA ET AL.: "Constitutive high-level production of human Lymphotoxin by CHO-K1 cells transformed with the human Lymphotoxin gene controlled by a human b-actin promoter" AGRICULTURAL AND BIOLOGICAL CHEMISTRY, vol. 55, no. 2, 1 February 1991, pages 501-508, XP000201543 see the whole document ----	1-6
A	US 5 378 603 A (UNIVERSITY OF TEXAS; BROWN M.S. ET AL. (US)) 3 January 1995 see column 36, line 41-68 ----	4
A	OSTADE VAN X. ET AL.: "Structure-activity studies of human Tumour Necrosis Factors" PROTEIN ENGINEERING, vol. 7, no. 1, 1 January 1994, pages 5-22, XP000421258 -----	

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IL 98/00254

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0168214	A	15-01-1986	US 4650674 A	17-03-1987
			AT 113295 T	15-11-1994
			AU 599571 B	26-07-1990
			AU 4465285 A	09-01-1986
			BG 60250 B	24-03-1994
			CZ 8505067 A	16-07-1997
			DE 3587939 D	01-12-1994
			DE 3587939 T	27-04-1995
			DK 75694 A	24-06-1994
			DK 169894 B	27-03-1995
			FI 852626 A,B,	06-01-1986
			FI 943750 A,B,	15-08-1994
			HR 950156 A	31-08-1997
			HU 209153 B	28-03-1994
			IE 65426 B	01-11-1995
			IL 75717 A	28-11-1994
			IL 105271 A	31-07-1995
			JP 7291997 A	07-11-1995
			JP 2614989 B	28-05-1997
			JP 8003061 A	09-01-1996
			JP 2557341 B	27-11-1996
			JP 61040221 A	26-02-1986
			JP 9028387 A	04-02-1997
			KR 9310767 B	10-11-1993
			MX 9203709 A	01-09-1992
			PT 80758 B	30-09-1987
			SI 8511132 A	31-10-1996
			US 5672347 A	30-09-1997
			US 5795967 A	18-08-1998
			RU 2076151 C	27-03-1997
			PH 25671 A	04-09-1991
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WO 8806625	A	07-09-1988	AU 1346488 A	26-09-1988
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US 5378603	A	03-01-1995	US 5527690 A	18-06-1996
			US 5256545 A	26-10-1993
			US 5215910 A	01-06-1993
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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>IPL-8 PCT</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/IL98/00254</b>	International filing date ( <i>day/month/year</i> ) <b>01/06/1998</b>	Priority date ( <i>day/month/year</i> ) <b>02/06/1997</b>
International Patent Classification (IPC) or national classification and IPC <b>C12N15/28</b>		
Applicant <b>INTERPHARM LABORATORIES LTD. et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 9 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I    ☒ Basis of the report
- II   ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV   ☐ Lack of unity of invention
- V    ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI   ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  <b>20/12/1998</b>	Date of completion of this report  <b>30.08.99</b>
Name and mailing address of the international preliminary examining authority:   <b>European Patent Office</b> <b>D-80298 Munich</b> <b>Tel. (+49-89) 2399-0 Tx: 523656 epmu d</b> <b>Fax: (+49-89) 2399-4465</b>	Authorized officer  <b>Julia, P</b>  Telephone No. (+49-89) 2399 8410  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL98/00254

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

### Description, pages:

1-39 as originally filed

### Claims, No.:

1-6 as originally filed

### Drawings, sheets:

1/7-7/7 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
  - ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/IL98/00254

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Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6.

because:

☒ the said international application, or the said claims Nos. 6 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL98/00254

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 1-5
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-5
Industrial applicability (IA)	Yes:	Claims 1-5
	No:	Claims

### 2. Citations and explanations

**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**1. Additional remarks to item II :**

The priority documents pertaining to the present application were not available at the time of establishing this international preliminary examination report (IPER). Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (02.06.97).

**2. Additional remarks to item III :**

The subject matter of **claim 6** is directed to a method for treatment of the human or animal body and thus, excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT. Furthermore, the attention of the Applicant is also drawn to the fact that for such a subject matter no unified criteria exist in PCT for the assessment whether it is industrially applicable or not. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**3. Additional remarks to item V :**

The present application discloses the production of recombinant human tumour necrosis factor  $\alpha$  (rhTNF- $\alpha$ ) in Chinese hamster ovary cells (CHO) and the purification and isolation of the resulting mixture comprising biologically active unglycosylated and glycosylated (about 35%) rhTNF- $\alpha$ . The description partially characterizes said glycosylated rhTNF- $\alpha$ , as being a glycoprotein with O-linked oligosaccharide comprising the monosaccharides galactose amine, galactose and sialic acid in a ratio of 1:1:1.5. The rhTNF- $\alpha$  mixture is isolated using the following steps : filtration (clarification) and concentration, affinity chromatography column (with human TNF binding protein-1, TBP-1), concentration, dialysis to the final buffer and terminal filtration. The application further refers to possible advantages of said glycosylated rhTNF- $\alpha$  (increased half-life in body fluids, improved binding to receptors, better protected against proteases, etc...) as well as possible uses in the treatment of human diseases and conditions.

The following documents have been cited in the International Search Report (ISR) as being relevant for assessing the novelty and inventiveness of the claimed subject matter:

- i) J.H. Korn et al., Lymphokine Res. 1988, Vol. 7 (4), pages 349-358 (**D1**) discloses the

production of rhTNF- $\alpha$  in CHO cells. There is no specific difference between the method disclosed in D1 (preparation of rhTNF- $\alpha$  using CHO cells as a host) and the one of the present application. Thus, the IPEA assumes that the product obtained in D1 must be glycosylated too and that there is no technical difference between the rhTNF- $\alpha$  of D1 and the rhTNF- $\alpha$  of the present application, i.e. D1 implicitly discloses a (inherently) glycosylated rhTNF- $\alpha$ . It is true that D1 is not aware of this glycosylation, however, the resulting product ("per se") is the same as well as the alleged therapeutic uses. The IPEA considers that the further characterization (determination of additional parameters) of a known product can not render such a product novel (this additional information does not change the product "per se" and in the present case it does not even provide a new use or application for this known product). D1 refers to the immunofluorescent localization of intracellular TNF- $\alpha$  as well as the identification of immunoreactive hTNF- $\alpha$  in culture supernatant of transfected cells (wherein the hTNF- $\alpha$  is immunoprecipitated and further denaturated). However, D1 clearly refers to the presence of hTNF- $\alpha$  activity in cell culture supernatant which are obtained by separation of the culture supernatant from cell culture and cell debris. In view of the ambiguous and broad interpretation of the wording "isolated" (see paragraph (iii) under "additional remarks to item VIII" below), the IPEA considers that **D1** anticipates the subject matter of **claims 1-2 and 4-5** (Articles 33 (2) and (3) PCT). In addition, the IPEA also considers that the skilled person would further purified the rhTNF- $\alpha$  from D1 so as to be suitable for the mentioned therapeutic uses. Thus, the subject matter of **claim 3** does not fulfil the requirements of Article 33 (3) PCT.

ii) EP-A-0 168214 (**D2**) discloses the production and characterization of rhTNF- $\alpha$ . Even if D2 explicitly refers to the possible absence of glycosylation (page 12, lines 25-30), the document explicitly refers to the production of rhTNF- $\alpha$  using general eukaryotic host cells including CHO cells (page 26 lines 18-20) and it further exemplifies the production of rhTNF- $\alpha$  using CHO cells (example 26, page 68). In agreement with the arguments cited on paragraph (i) above, the IPEA considers that D2 implicitly anticipates the mixture of glycosylated and unglycosylated rhTNF- $\alpha$  of the present application. Thus, the subject matter of **claims 1-5** does not fulfil the requirements of Articles 33 (2) and (3) PCT.

The attention of the Applicant is also drawn to the fact that according to the description, the general wording "human tumour necrosis factor" used in the claims must be read as meaning "human tumour necrosis factor- $\alpha$ " which, however, embraces mutants, derivatives and/or variants thereof too (pages 33-35). D2 explicitly discloses different

hTNF- $\alpha$  derivatives which are so constructed as to be glycosylated (page 15 lines 32 - page 16 line 15, page 66 lines 29-31). In the light of the present description, these derivatives would be embraced by the wording of the claims and thus, they would be novelty destroying for the subject matter of claims 1-5 (Articles 33 (2) and (3) PCT). This interpretation applies for the teachings of the document WO-A-88/06625 (**D3**) too, which discloses the production of glycosylated rhTNF- $\alpha$  derivatives (Articles 33 (2) and (3) PCT).

iii) K. Nakagawa et al., Agricultural and Biological Chemistry 1991, Vol. 55 (2), pages 501-508 (**D4**) discloses the production and isolation (cell supernatant) of rhTNF- $\beta$  in CHO-K1 cells. D4 explicitly emphasizes the relevance and importance of the carbohydrate groups for the full spectrum of biological activity (page 501). In view of the wording "human tumour necrosis factor" used in the claims (see paragraph (ii) under "Additional remarks to item VIII" below), the IPEA considers that such wording embraces the product disclosed in D4 and thus, **claims 1-5** do not fulfil the requirements of Articles 33 (2) and (3) PCT.

iv) in view of the arguments cited above (in particular in respect of the wording "human tumour necrosis factor" and "isolated" as well as in respect of the characterization of a product by disclosing additional inherent features of a known product), the IPEA considers that the document US-A-5 378 603 (**D5**), which discloses the production of "human tumour necrosis factor" in CHO cells (example IV), is also novelty destroying for the subject matter of **claims 1-5** (Articles 33 (2) and (3) PCT).

#### **4. Additional remarks to item VIII :**

The following objections are also raised under **Article 6 PCT** concerning the clarity of the claims :

i) according to Article 6 PCT in combination with Rule 6.3 PCT the claims shall define the matter for which protection is sought in terms of technical features. The IPEA considers that a peptide, polypeptide or protein being chemical products must be clearly and unambiguously characterized by their amino acid and/or nucleic acid sequences, i.e. by reference to their specific SEQ ID No. Furthermore, the characterization of a product only by a desired feature ("glycosylated") but without any actual (technical) characterization, such as being a glycoprotein with O-linked oligosaccharide, monosaccharide

composition and corresponding ratio, glycosylation pattern, etc... does not fulfill the requirements of said Article 6 PCT in combination with Rule 6.3 PCT. Thus, the subject matter of **claim 1** is considered to be worded only in terms of the result to be achieved.

ii) the wording of the claims must be clear, consistent and coherent "per se". The IPEA considers that the general wording "human tumour necrosis factor" (hTNF) as used in the claims embraces both hTNF- $\alpha$  (cachectin) and hTNF- $\beta$  (lymphotoxin), even if in the description explicit mention is made that it is intended to embrace only hTNF- $\alpha$  (page 6 lines 5-7). In addition, this wording is not restricted to "recombinant" TNF but it certainly includes "natural" or "non-recombinant" TNF. However, the IPEA considers that it does not embrace biologically active TNF fragments, TNF mutants or variants thereof, etc... as it seems to be implied by pages 33-35 of the description.

iii) in the light of the results disclosed in the description and in particular the fact that what is actually "isolated" is a mixture of unglycosylated (main peak) and glycosylated (only about 35% !!!) rhTNF- $\alpha$ , the interpretation of the wording "isolated" in **claims 1 and 2** is ambiguous. There is no actual "isolation" of any glycosylated hTNF- $\alpha$  in the application, in the sense that there is no disclosure of any pure and homogenous glycosylated hTNF- $\alpha$ , i.e. without any presence of unglycosylated rhTNF- $\alpha$ . In this respect, part (d) of claim 2 refers to the "isolation" of the glycosylated hTNF, whereas claim 3 refers to a further purification of the "isolated" glycosylated hTNF.

iv) the IPEA considers that the general wording "physiologically active variant of human TNF" is ambiguous as far as it is not restricted or limited to any specific number and type of mutations, modifications, etc..., i.e. it is open-ended (any protein can be derived from another one by a suitable number and type of mutations). In this respect, human (glycosylated) TNF- $\beta$  or (glycosylated) rat TNF- $\alpha$  could be seen as "variants" of human TNF- $\alpha$  too. Thus, the actual scope of claim 2 (directed to the preparation of glycosylated "hTNF" but referring to a DNA encoding general "hTNF variants") is ambiguous.

v) in addition, as far as there is no full or complete characterization of the glycosylated rhTNF- $\alpha$  produced in CHO cells (i.e. the determination and characterization of the specific residues of the amino acid sequence of the hTNF- $\alpha$  which are glycosylated as well as their carbohydrate composition, etc...), the IPEA considers that the referred "glycosylated hTNF- $\alpha$  variants, fragments and mutants" are only a "result to be achieved", in the sense that

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EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/IL98/00254

there is no technical information in the application which could allow the skilled person to achieve them in an obvious way.

vi) the attention of the Applicant is also drawn to the fact that **claim 2** is not directed to the production or preparation of "biologically active" hTNF. This claim is directed to the preparation of "glycosylated hTNF" and there is one reference to a "physiologically active" variant of hTNF. However, this reference is only optional ("or") and there is no requirement that on step (d) of claim 2 said "physiological activity" must be still present.

# TENT COOPERATION TREATY

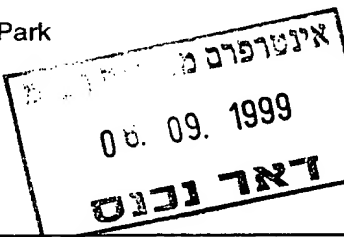
From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

## PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

To:

EINAV, Henry  
Inter-Lab Ltd.  
Science-based Industrial Park  
Kiryat Weizmann  
76110 Ness-Ziona  
ISRAEL



Date of mailing  
(day/month/year) **3 0. 08. 99**

Applicant's or agent's file reference  
IPL-8 PCT

### IMPORTANT NOTIFICATION

International application No.  
PCT/IL98/00254

International filing date (day/month/year)  
01/06/1998

Priority date (day/month/year)  
02/06/1997

Applicant  
INTERPHARM LABORATORIES LTD. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

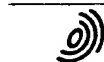
#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. (+49-89) 2399-0 Tx: 523656 epmu d  
Fax: (+49-89) 2399-4465

Authorized officer

Peralt Lappas, R

Tel. (+49-89) 2399-8052

